REMARKS

Claims 90-102 have been canceled. New claims 103-110 have been added and are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claim 90-102 under 35 U.S.C. § 101

Claims 90-102 stand rejected under 35 U.S.C. § 101 on the ground that the claimed invention lacks patentable utility for reasons of record. The Office Action of February 25, 2002 stated:

> The claimed combination of nucleic acids is not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. The disclosed utility is to use an array of *Aspergillus oryzae* ESTs to determine expression profiles that are correlated with different types of cells or different growth states of cells. No evidence has been disclosed that the elected SEQ ID NOS allow for determination of the state or type of cell that is assayed by the claimed method of using an array of *Aspergillus oryzae* ESTs. Further research is required to determine whether the claimed method utilizes ESTs that allow for useful discrimination between cell types or cell states. The research required to establish the utility of the claimed method is not consistent with a substantial utility. Identifying and studying the properties of an array of ESTs does not define a "real world" context or use. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the array of ESTs such that another non-asserted utility would be well established for the compounds.

This rejection is respectfully traversed.

Applicants disagree with the Office Action's statement that the "claimed combination of nucleic acids is not supported by a substantial utility" because "[n]o evidence has been disclosed that the elected SEQ ID NOS allow for determination of the state or type of cell that is assayed by the claimed method of using an array of *Aspergillus oryzae* ESTs."

Based on Applicants' specification and Examples, particularly Example 16, one of ordinary skill in the art would recognize that the claimed method using an array of *Aspergillus oryzae* ESTs allows for a determination of the global expression of genes of a filamentous fungal cell. Applicants provide detailed protocols for monitoring differential expression of a plurality of genes in a filamentous fungus of interest. These protocols include a set of *Aspergillus oryzae* EST sequences with their nucleic acid sequences and function identified (see Table 3; page 4, line 28, to page 7, line 7); methods and instruments for forming microarrays on the surface of a solid support (see page 7, line 9, to page 11, line 3); preparation of nucleic acid probes from filamentous fungi and

their labeling with reporters, e.g., Cy3 and Cy5 (see page 11, line 5, to page 13, line 9); hybridization of the probes with the arrays containing the *Aspergillus oryzae* ESTs (see page 13, line 11, to page 24, line 24; and methods of detection and data analysis (see page 14, line 26, to page 15, line 21). These detailed protocols provide one of ordinary skill in the art with methods for monitoring the global expression of genes from filamentous fungal cells. Monitoring global expression can be used, for example, to improve the production potential of a microorganism.

Example 16 of the specification is an example of monitoring multiple changes in expression of *Fusarium venenatum* genes to specifically identify those genes whose expression (a) increases by a factor of approximately two, (b) remains the same, or (c) decreases by a factor of approximately two in response to the presence of maltose as a sole carbon source. *Fusarium venenatum* strain CC1-3 was grown in Vogel's minimal medium with either 2% glucose or 2% maltose as the sole carbon source. After 2 days growth at 28°C, total RNA and mRNA pools were purified from each culture. PolyA-selected mRNA was used as a template to prepare fluorescently labeled probes for hybridization. In this experiment, the probes from glucose-grown cells were labeled with Cy3 and the probes from maltose-grown cells were labeled with Cy5. The probes were combined and hybridized with the 1152 EST targets on the microarray. After hybridization and washing, the microarrays were scanned (see Example 15), and the images analyzed using ScanAlyze software (see Example 15) to determine the relative ratios of red and green fluorescence in each spot on the arrays. A number of genes satisfying the above criteria were readily identified as shown in Table 5. A person of ordinary skill in the art would be able to perform the same experiment on *Aspergillus oryzae* using the ESTs of SEQ ID NOs. 4377-7401 by following the detailed protocols provided by the Applicants.

As stated in Applicants' amendment of August 23, 2002, one of ordinary skill in the art using Applicants' disclosure would be able to set-up and use the methods of the present invention to monitor global expression of a plurality of genes from a filamentous fungal cell with respect to a particular phenotype such as improved secretion or production of a protein or compound, reduced or no secretion or production of a protein or compound, improved or reduced expression of a gene or pathway, desirable morphology, an altered growth rate under desired conditions, relief of over-expression mediated growth inhibition or tolerance to low oxygen conditions; to discover new genes; to identify possible functions of unknown open reading frames; and to monitor gene copy number variation and stability. For example, the global view of changes in expression of genes may be used to provide a picture of the way in which filamentous fungal cells adapt to changes in culture conditions, environmental stress, or other physiological provocation. Applicants also provide other possibilities for monitoring global expression include spore formation/germination, recombination, metabolic or catabolic pathway engineering.

The Office Action also states "[i]dentifying and studying the properties of an array of ESTs does not define a 'real world' context or use." Applicants respectfully disagree with this statement because the present invention is not directed to identifying and studying the properties of an array of ESTs, but rather to use an array of *Aspergillus oryzae* ESTs to determine expression profiles of a plurality of genes that correlate, for example, with adaptation to changes in culture conditions, environmental stress, or other physiological provocation of a filamentous fungal cell of interest. Moreover, one spot on an array corresponds to one gene or open reading frame; extensive follow-up characterization is unnecessary since sequence information is available as shown in Table 3 of the specification, and EST microarrays can be organized based on function of the gene products. Applicants provide in Table 3 annotated identification of the open reading frames of the *Aspergillus oryzae* ESTs. It is well within the skill in the art to use Applicants' disclosure to monitor the global expression of a plurality of genes from a filamentous fungal cell with respect to any of the above-noted phenotypes.

Applicants assert, therefore, that the claimed method using the combination of nucleic acids is supported by a substantial patentable utility.

For the foregoing reasons, Applicants submit that the rejection under 35 U.S.C. § 101 has been overcome and respectfully request reconsideration and withdrawal of the rejection.

II. The Rejection of Claims 90-102 under 35 U.S.C. § 112, First Paragraph

Claims 90-102 stand rejected under 35 U.S.C. § 112, first paragraph, on the ground that one skilled in the art would not know how to use the claimed invention since it is not supported by a substantial utility or a well established utility, as described in Section I. This rejection is respectfully traversed.

Based on Applicants' arguments in Section I, Applicants assert that one skilled in the art would know how to use the claimed invention because it is supported by a substantial utility.

For the foregoing reason, Applicants submit that the rejection under 35 U.S.C. § 112 has been overcome and respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 90-102 under 35 U.S.C. § 112, First Paragraph

Claims 90-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record. The Office Action of February 25, 2002 stated:

> The specification discloses SEQ ID NO: 4377-7401. SEQ ID NO: 4377-7401 meet the written description provisions of 35 USC 112, first paragraph. However, because it is not apparent that SEQ ID NO: 4377-7401 comprises a complete

> open reading frame, claim 20 is directed to encompass gene sequences and complete cDNA sequences due to the recitation of the phrase "and nucleic acid sequences having at least 90% homology to SEQ ID NOS: 4317-7401." The claims further encompass sequences that hybridize or are similar to SEQ ID NO: 4377-7401, corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. None of these sequences meet the written description provision of 35 U.S.C 112, first paragraph.

This rejection is respectfully traversed.

The Office Action of February 25, 2002 stated that while SEQ ID NOs: 4377-7401 meet the written description provisions of 35 U.S.C. 112, first paragraph, sequences that have a recited degree of homology do not meet the written description requirement. Applicants respectfully disagree with this assertion because at least 90% homology dictates that all species within the genus will be structurally similar. Applicants detail on page 7, lines 2-7, of the specification, that the degree of homology between two nucleic acid sequences is determined by the Wilbur-Lipman method (Wilbur and Lipman, 1983, *Proceedings of the National Academy of Science USA* 80: 726-730). However, to further prosecution, Applicants have amended the claims not to recite percent homology.

For the foregoing reasons, Applicants submit that the new claims overcome the rejections under 35 U.S.C. § 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Robert L. Starnes

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Robert L. Starnes, Reg. No. 41,324
Novozymes Biotech, Inc.
1445 Drew Avenue
Davis, CA 95616-4880
(530) 757-4715